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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,880	07/10/2003	Benjamin David Silverman	YOR920030162US1	2640

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RYAN, MASON & LEWIS, LLP
1300 POST ROAD
SUITE 205
FAIRFIELD, CT 06824

EXAMINER	
NEGIN, RUSSELL SCOTT	

ART UNIT	PAPER NUMBER
1631	

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10/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/616,880	SILVERMAN, BENJAMIN DAVID	
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-9,14,15,17 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-9,14,15,17 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

The finality of the previous action is withdrawn in view of the additional ground of rejection.

Applicants' amendments and request for reconsideration in the communication filed on 3 October 2008 are acknowledged and the amendments are entered.

Claims 1, 3-5, 7-9, 14-15, 17, are 19-21 are pending, and examined in this Office action.

Claim Rejections - 35 USC § 101

The following 35 U.S.C. 101 Rejections are newly applied:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3-5, and 7-9 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The method claims of the instant application (instant claims 1, 3-5, and 7-9) recite a series of steps without a physical transformation. Further, the claims fail to recite a tie to another statutory class of invention. It is noted that while the result of the calculation is output to a user, this final step is an insignificant post-solution activity and does not constitute a significant tie to another category of invention.

Claim Rejections - 35 USC § 103

The following 35 U.S.C. 103 Rejection is reiterated:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, 7-9, 14-15, 17, and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eisenberg et al. [Nature, volume 299, 1982, pages 371-274] in view of Silverman [PNAS; April 24, 2001; volume 98, pages 4996-5001].

Claim 1 is drawn to a method for calculating a global hydrophobic moment of a tertiary protein structure comprising a plurality of residues, the method comprising the steps of:

--calculating a centroid of residue centroids;

--using the centroid of residue centroids as a spatial origin of a global linear hydrophobic moment;

--calculating a first-order hydrophobic moment;

--enhancing correlation between residue centroid magnitude and residue solvent accessibility, wherein the correlation between residue centroid magnitude and residue solvent accessibility is enhanced using a distance metric;

--using the first order hydrophobic moment and the enhances correlation between residue centroid magnitude and residue solvent accessibility to define a global linear

hydrophobic moment, wherein each of the residue centroids contributes a magnitude and direction to the global hydrophobic moment;

--using the global linear hydrophobic moment to characterize an amphiphilicity of a tertiary protein structure; and

--outputting the global linear hydrophobilc moment to at least one or a user, a display, a memory and one or more additional computers on a network.

Claim 14 is drawn to the same subject matter as claim 1 wherein an apparatus is used fro executing the method.

Claim 21 is drawn to the same subject matter as claim 1 wherein an article of manufacture is used for calculating a global hydrophobic moment of a tertiary protein structure.

Claims 3-4 and claims 19-20 are further limiting with the additional limitations that the correlation between the residue centroid magnitude and the residue solvent accessibility is enhanced by using an ellipsoidal metric and a solvent accessibility metric, respectively.

Claim 5 and claim 15 are further limiting with the additional limitation that the centroid of residue centroids represents a geometric center of the tertiary protein structure.

Claims 7-9 and claim 17 are further limiting with the additional limitations that the global linear hydrophobic moment characterizes the magnitude of amphiphilicity, direction of amphiphilicity, and identification of functional regions in the tertiary protein structure, respectively.

The article of Eisenberg et al. studies use of a first order helical hydrophobic moment to measure the amphiphilicity of a helix.

The abstract on page 371 of Eisenberg et al. quantifies the mean hydrophobic moment as a vector sum of all of the first order hydrophobic moments of the residues constituting the helix.

Figure 1 of page 372 of Eisenberg et al. illustrates a vector sum for a helix to determine a global (i.e. mean) hydrophobic moment for a protein helix. Each residue in the helix contributes a magnitude and direction of the global hydrophobic moment.

Figure 1 is also an output of the global linear hydrophobic moment for an alpha helix.

Figure 2 on page 374 of Eisenberg et al. plots the hydrophobic moments of helices of different proteins as a function of the degree of hydrophobicity/amphiphilicity of each of the helices in the study. It is also noted that the plot in Figure 2 of Eisenberg et al. displays the magnitude of the first-order hydrophobic moment as a function of the hydrophobicity which is defined as the equivalent of a zero order (linear) hydrophobic moment in Eisenberg et al. (i.e. see second full paragraph in column 2 of Eisenberg et al. on page 372).

However, Eisenberg et al. does not use residue centroids as the origins in the hydrophobic moment calculations (instead, alpha carbons are used as reference points), Eisenberg et al. does not show correlation enhancement between residue centroid magnitude and solvent accessibility, and Eisenberg et al. does not show the computer hardware and software limitations of the instant claims.

The article of Silverman, "Hydrophobic moments of protein structures: Spatially profiling the distribution," describes how to calculate moments of tertiary protein structures.

In equation [12] on page 4997 of Silverman, r_i is the vector pointing to the centroid of residue *i* while r_c is the vector pointing to the centroid of the entire protein molecule (i.e. the geometric center of the protein).

In equation [13] on page 4998 of Silverman, a first order hydrophobic moment imbalance about the entire protein is derived, accounting for hydrophobicity and solvent accessible surface area. Each centroid of every protein residue contributes to this global moment.

In equations [13] and [14] on page 4998 of Silverman, distance metrics, ellipsoidal metrics, and a solvent accessibility are all used to enhance the centroid magnitude.

Pages 4998-5000 of Silverman illustrate the computation of global linear (i.e. zero order) hydrophobic moments for entire proteins.

Additionally, page 4998, column 2 teaches the obtaining of protein structures from the Internet, and page 5000, column 2, paragraph 2 teaches obtaining protein structures from the PNAS website.

Figure 6 on page 5000 of Silverman shows how an arm of the protein can be identified as it falls outside the ellipse characterizing the hydrophobic moment of the protein.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the helical hydrophobic moment study of Eisenberg et al. by use of the hydrophobic moment study of Silverman wherein the motivation would have been that using residue centroids instead of atomic points yields a more ideal overall shape and moment of the protein (see first full paragraph of column 1 on page 4998 of Silverman). Additionally, automation of the process of Eisenberg et al. on the internet provides a faster and more efficient means of executing the claimed invention. There would have been a reasonable expectation of success in applying the moment analysis of a single helical secondary structure to the entire protein structure because the mathematical vector analysis is general and not locally restricted to single secondary structural elements.

Response to Arguments:

Applicant's arguments filed 3 October 2008 have been fully considered but they are not persuasive.

Applicant argues that Silverman does not teach or suggest the limitation of enhancing correlation between residue centroid magnitude and residue solvent accessibility, wherein the correlation between the residue centroid magnitude and residue solvent accessibility is enhanced using a distance metric. This is not persuasive because , as discussed above, while Silverman teaches residue centroids, Eisenberg uses centers of residues (at alpha carbons) to calculate first order hydrophobic moments (using distances) with magnitudes plotted on the ordinate axis of

Figure 2 of Eisenberg et al. Using this ordinate coordinate and the curve illustrated in Figure 2, one of skill in the art can calculate the hydrophobicity (or the zero order hydrophobic moment) of the helix (i.e. the zero order hydrophobic moment is also linear). Silverman expands this analysis for calculating the zero order linear hydrophobic moment for an entire protein.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation is stated above and reiterated below:

> It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the helical hydrophobic moment study of Eisenberg et al. by use of the hydrophobic moment study of Silverman wherein the motivation would have been that using residue centroids instead of atomic points yields a more ideal overall shape and moment of the protein (see first full paragraph of column 1 on page 4998 of Silverman). Additionally, automation of the process of Eisenberg et al. on the internet provides a faster and more efficient means of executing the claimed invention. There would have been a reasonable expectation of success in applying the moment analysis of a single helical secondary structure to the entire protein structure because the mathematical vector analysis is general and not locally restricted to single secondary structural elements.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the

central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/RSN/
Russell S. Negin, Ph.D.
22 October 2008

/Marjorie Moran/
Supervisory Patent Examiner, Art Unit 1631